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August 4, 1977

"Cigarette smoking, use of oral contraceptives, and mycardial infarction," Anrudh K. Jain, American Journal of Obstretics and Gynecology, Vol. 126, No. 3, October 1976, pp. 301-307.

This paper is one of the most frustrating I have ever tried to read with understanding. The author uses no data of his own. Instead, he interprets the results of his arithmetic manipulations of other peoples' data, especially those of Mann et al (1). In so doing, however, he often refers to "Columns 1 and 4 in Table 1." I was startled to find that no such table exists either in Jain's document or in the one by Mann et al (1). This, in itself, is a sad commentary on the editorial and review procedures of the Amer. J. of Obst. & Gyn.

Reproduction of all the numerical results in this document is essential to a complete understanding of Jain's arguments. Let us begin with Table VIII of the paper by Mann et al (1). This table may be summarized as follows:

| | Myocardial Infarction | | | Control | | |
	No pill	Pill	Total	No pill	Pill	Total
Nonsmoker	13	3	16	70	8	78
Smoker	28	13	41	70	6	76
Total	41	26	57	140	14	154

In the study by Mann et al (1), "63 women discharged from hospital with a diagnosis of myocardial infarction and 189 control patients were studied." Of these 252 women, 41 are omitted from this analysis for one reason or another (for example, 21 had died

in hospital or shortly after release from hospital). Smoking histories were considered by Mann et al (1) because, "...in Britain oral contraceptive use is associated with cigarette smoking, and cigarette smoking is associated with myocardial infarction." With respect to their actual samples, Mann et al (1) also note that, "Cigarette smoking was reported more often by patients with infarction than by controls, which was due almost entirely to the inclusion of a large excess of moderate and heavy smokers." An earlier table in the paper indicates that 56.2% of the infarct patients, and 21.1% of the control patients smoked 15 or more cigarettes per day.

In his discussion of the effect of smoking Jain refers to the data presented above. He says:

1. "...the relative risk of nonfatal myocardial infarction among those who only use oral contraceptives is about the same as the relative risk among those who only smoke."

Interpretation: 3 out of 57 infarct patients use the pill and don't smoke compared with 8 out of 154 control patients in the same category:

$$\frac{3}{57} \Big/ \frac{8}{154} = 1.01$$

28 out of 57 infarct patients smoke and are not on the pill compared with 70 out of 154 control patients in the same category:

$$\frac{28}{57} \Big/ \frac{70}{154} = 1.08$$

2. "The risks among women in these two groups are estimated to be about twice as high as those who neither use oral contraceptives nor smoke cigarettes."

Interpretation: 13 out of 57 infarct patients neither smoke nor are on the pill compared with 70 out of 154 control

patients in the same category:

$$\frac{13}{57} \Big/ \frac{70}{154} = 0.5$$

The earlier numbers (risks?) are about twice as large as this one.

3.   "The relative risk associated with the use of oral contraceptives alone is not statistically significant ($P = 0.28$, Fisher's exact probability test) whereas the relative risk associated with smoking alone is statistically significant ($P = 0.029$, Fisher's exact probability test)."

Interpretation: I have not been able to verify this statement with the data from Table VIII of Mann et al (1). It might be based on an analysis of data from Table X. Jain refers to this table in an earlier paragraph where he makes the following assertions:

4.   "...it can be estimated that in comparison with women not known to have any risk factors the relative risk of nonfatal myocardial infarction in women using oral contraceptives alone is 1.5 to 1..."

"...and that associated with cigarette smoking alone can be estimated to be 3.5 to 1."

Interpretation: Of 60 infarct patients, eleven had no risk factors, seven smoked 15 cigarettes or more per day and had no other risk factors, and one was a current user of oral contraceptives and had no other risk factors. These figures are compared with 173 control patients, of whom 115, 21, and 7 respectively were in the three specific categories of interest. Thus:

$$\frac{1}{11} \Big/ \frac{7}{115} = 1.5,$$

$$\frac{7}{11} \Big/ \frac{21}{115} = 3.5$$

I cannot reproduce the probabilities associated with the "Fisher exact test." By this, I do not imply that Jain is wrong. I merely do not know which numbers he has used in applying the Fisher test.

5. "The relative risk among those who use oral contraceptives as well as smoke is estimated to be 11.7 to 1."

Interpretation: 13 out of 57 infarct patients smoke and are on the pill, and another 13 out of 57 neither smoke nor use the pill. These numbers compare with 6 out of 154 and 70 out of 154 control patients respectively.

$$\frac{13}{13} \Big/ \frac{6}{70} = 11.67$$

Comment: Use of the term "relative risk" here and elsewhere in this study, as in many others is ill-conceived. In this instance, among 57 infarct patients 13 neither smoked nor used the pill, and 13 both smoked and used the pill. Thus, the proportions of such infarct patients are observed to be equal. By the same token, among 154 patients in hospital with other problems, the proportions with these characteristics have been observed to be 6/154 and 70/154 respectively. Personally, I would feel much more comfortable concluding that the 154 patients with other problems are not a proper control for the groups of infarct patients. The general use of patients in hospital as subjects in studies of this type was questioned by Berkson many years ago. Moreover, designating this variability in relative frequencies as a "risk" or a "relative risk" stretches the imagination beyond the breaking point. The absurdity of this type of analysis may be vividly portrayed by the application of these same interpretive techniques to the results of public opinion polls.

6. "The relative risk of nonfatal myocardial infarction associated with the use of oral contraceptives among smokers can be estimated to be 5.4 to 1 (11.67 to 2.15)."

Interpretation: Among the 154 control patients 140 were not on the pill. 70 of these were nonsmokers and 70 were smokers. Among the 57 infarct patients 41 were not on the pill. 13 of these were nonsmokers and 28 were smokers.

$$\frac{70}{70} \Big/ \frac{13}{28} = 2.15$$

Among the 76 control patients who smoked, 6 were on the pill and 70 were not. Among the 41 infarct patients who smoked 13 were on the pill and 28 were not.

$$\frac{13}{28} \Big/ \frac{6}{70} = 5.42$$

This is identically equal to the ratio 11.67/2.15.

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7.   "The corresponding risk associated with smoking among users can be estimated to be 5.8 to 1 (11.67 to 2.02)."

Interpretation: Among the 78 nonsmoking controls, 8 were on the pill and 70 were not.   Among the 16 nonsmoking infarct patients 3 were on the pill and 13 were not.

$$\frac{3}{13}\bigg/\frac{8}{70} = 2.02$$

Among the 14 control patients on the pill 8 were nonsmokers. Among the 26 infarct patients on the pill 3 were nonsmokers and 13 were smokers.

$$\frac{8}{6}\bigg/\frac{3}{13} = 5.8 \; ,$$

which is identically equal to the ratio, 11.67/2.02.

8.   The data dealing with the joint effect of heavy smoking and oral contraceptions on myocardial infarction also appear in Table VIII of Mann et al (1):

	Myocardial Infarction			Control		
	No pill	Pill	Total	No pill	Pill	Total
Nonsmoker	13	3	16	70	8	78
1-14/day	6	2	8	42	2	44
15+/day	22	11	33	28	4	32
Total	41	16	57	140	14	154

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Values of "relative risk" presented in Jain's Table 1 are calculated as follows:

	(Smoker + Pill) vs. (Nonsmoker + No pill)	(Smoker + No Pill) vs. (Nonsmoker + No Pill)
Total Smokers	$\dfrac{13}{13} \Big/ \dfrac{6}{70} = 11.67$	$\dfrac{28}{13} \Big/ \dfrac{70}{70} = 2.15$
Heavy Smokers	$\dfrac{11}{13} \Big/ \dfrac{4}{70} = 14.81$	$\dfrac{22}{13} \Big/ \dfrac{28}{70} = 4.23$
Light Smokers	$\dfrac{2}{13} \Big/ \dfrac{2}{70} = 5.38$	$\dfrac{6}{13} \Big/ \dfrac{42}{70} = 0.77$
Nonsmoker (Pill vs. No Pill)	$\dfrac{3}{13} \Big/ \dfrac{8}{70} = 2.02$	----
Heavy Smoker (Nonsmoker vs. Light Smokers)	$\dfrac{11}{19} \Big/ \dfrac{4}{112} = 16.21$	$\dfrac{22}{19} \Big/ \dfrac{28}{112} = 4.63$
Light Smokers & Nonsmokers (Pill vs. No Pill)	$\dfrac{5}{19} \Big/ \dfrac{10}{112} = 2.95$	----
Smokers & Nonsmokers (Pill vs. No Pill)	$\dfrac{16}{41} \Big/ \dfrac{14}{140} = 3.90$	----

Jain speaks only to a portion of these results. For example, he ignores the "relative risk" of 0.77 among light smokers who are not on the pill. One interpretation of this number following Jain's arguments, is that for women not on the pill, light smokers have a lower risk of nonfatal myocardial infarction than nonsmokers. Moreover, this lower relative risk increases the relative odds, beyond that of any other group, that light smokers on the pill will have a nonfatal myocardial infarction. To illustrate:

the relative risk of nonfatal myocardial infarction for nonsmokers is

$$\frac{3}{13} \Big/ \frac{8}{70} = 2.02;$$

for heavy smokers, it is

$$\frac{11}{22} \quad \frac{4}{28} = 3.5;$$

and for light smokers, it is

$$\frac{2}{6} \quad \frac{2}{42} = 7.0.$$

Jain does not explain this incongruity.

9. In general I would say that Jain has made much hay out of a trivial amount of data. His arithmetic manipulations appear to be correct. Nevertheless, his interpretation of the results of these manipulations in terms of "relative risks" and "odds ratios," and the application of statistical inference to these results are subject to serious fundamental questions.

(1) J. I. Mann, M. P. Vessey, Margaret Thorogood, and Sir Richard Doll, "Myocardial infarction in young women with special reference to oral contraceptives practice," British Medical Journal, 2, 1975, pp. 241-245.